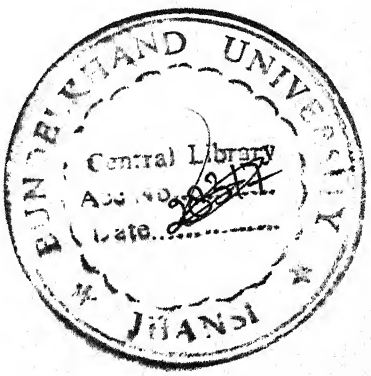
A COMPARATIVE EVALUATION OF SOYA BASED LACTOSE FREE FORMULA, AND PARENTERAL ANTIBIOTICS THERAPY IN MANAGEMENT OF SECONDARY LACTASE DEFICIENT CHRONIC DIARRHOEAL CASES

THESIS

FOR

DOCTOR OF MEDICINE

(PEDIATRICS)



BUNDELKHAND UNIVERSITY
JHANSI (U. P.)

1996 LALIT KUMAR

C E R T I F I C A T E

This is to certify that the work entitled "A COMPARATIVE EVALUATION OF SOYA BASED LACTOSE FREE FORMULA AND PARENTERAL ANTIBIOTIC THERAPY IN MANAGEMENT OF LACTASE DEFICIENT CHRONIC DIARRHOEAL CASES", which is being submitted as a thesis for M.D.(Pediatrics) Examination, 1996 of Bundelkhand University, Jhansi, has been carried out by Dr. Lalit Kumar in the Department of Pediatrics, M.L.B. Medical College, Jhansi.

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न हि ज्ञानेन सदृशं पवित्रमिह विद्यते ।
तत्स्वयं योगसंसिद्धः कालेनात्मनि विन्दति ।। 38 ।।

श्रीमद्भगवद्गीता अध्याय-4

डा० अनिल कौशिक एम०डी० का मैं विशेष रूप से ऋणी हूँ जिन्होनें अपनी बेबाक आलोचनाओं द्वारा शोध कार्य के दौरान आई शैक्षणिक अड़चनों को दूर करते हुये इस महत्वपूर्ण कार्य को संपन्न कराने में महती भूमिका निभाई ।

मैं डा० एस०पी० सिंह पी०एच०डी० सह आचार्य जैव रसायन विभाग महारानी लक्ष्मीबाई मेडिकल कालेज का सदैव आभारी रहूँगा जिनके सतत् मार्ग दर्शन के फलस्वरूप यह शोध कार्य अपने वर्तमान स्वरूप को प्राप्त कर सका ।

मैं डा० आर० के० अग्रवाल एम०डी० सह आचार्य माइक्रोबायलोजी विभाग का भी विशेष आभारी रहूँगा जिनके मार्ग दर्शन से शोध कार्य में आयी बाधाओं को पार करते हुये अपने कार्य को वर्तमान स्वरूप दे सका ।

अपने अभिन्न मित्र श्री जी०पी० गुप्ता प्रदर्शक जैव रसायन विभाग के सहयोग का आभार शब्दों में व्यक्त कर पाना मेरे लिए सम्भव नहीं है । जिन्होनें क्रोमेटोग्राफी का प्रारूप समझाया एवं मेरे प्रयोगात्मक कार्य में सहायता की ।

वर्तमान शोध कार्य में सहयोग प्रदान करने के लिये, अपने कनिष्ठ सहयोगियों डा० प्रशांत, डा० अनिल, डा० सुरेश, डा० कमल, डा० दीपक एवं डा० अनिता व विभाग के अन्य सहयोगियों का विशेष रूप से आभार ज्ञापित करता हूँ, जो ऐसे अवसरों पर संबल बने जब मैं खुद को अंधकार में पाता था ।

यदि इस अवसर पर मैं श्री फूल चन्द्र सचान का नाम नहीं लूँ तो मुझे यह शोध प्रबन्ध अधूरा सा प्रतीत होगा । उनके त्रुटिहीन टंकण ने इस शोध प्रबन्ध को एक अद्भुत गरिमा प्रदान की ।

अन्त में उन समस्त सुकोमल शिशुओं एवं उनके धैर्यशाली अभिभावकों को कोटिशः धन्यवाद देता हूँ जिनके सहयोग के बिना यह शोध कार्य पूर्ण करना असम्भव था ।

Kumar.

ललित कुमार

C O N T E N T

I N T R O D U C T I O N

INTRODUCTION

Diarrhoeal disease is one of the leading causes of morbidity and mortality among infants and preschool children in developing countries. Majority of the diarrhoeal episodes are acute and self limiting. Protracted diarrhoea is defined as persistence of diarrhoea beyond 2 weeks with at least 4 liquid stools per day, with no weight gain or with weight loss and where conventional line of treatment has failed.

Chronic diarrhoea is an important major problem among infants and children in developing countries. In rural north India, nearly half of all diarrhoea deaths in children upto 5 years of age are related to chronic diarrhoea. Persistence diarrhoea is associated with deterioration in nutritional status and substantial risk of death.

Persistent diarrhoea was arbitrarily defined as diarrhoea of a presumed infectious cause that begins acutely and lasts for 14 days or more. The 14 day cutt-off is consistent with significant increase in mortality for episodes longer than 14 days than for those that lasted between 7-14 days in Indian cohort study (Bhan et al, 1986).

Three to twenty percent of acute diarrhoeal episodes in children in developing countries are persistent.

There are various causes of protracted diarrhoea. For example - infection, enzyme deficiency, inflammatory

bowel disease, metabolic disorder, villous atrophy due to any cause etc. But in about 30% of infants with diarrhoea, the etiology in unknown. In our country, the carbohydrate intolerance and milk protein intolerance are the commonest causes of protracted diarrhoea. The basic hallmark of protracted diarrhoea is a persistent mucosal injury. Several secondary factors, supervene the mucosal abnormalities and lead to vicious cycle of diarrhea.

Malabsorption ---- Malnutrition --- diarrhoea.

Various causes of diarrhoea

- Persistence of colonization of upper small intestine by microbes.
- Dietary allergy, specially to gluten.
- Carbohydrate intolerance because of intestinal damage resulting in low level of disaccharidases.
- Decreased host immunity such as after an attack of measles.
- Poor hygienic conditions.
- Protozoal infection.
- Inflammatory bowel diseases.
- Deficiency of pancreatic enzymes.
- Metabolic disorders.
- Primary congenital deficiency of disaccharidases.

Alteration in digestion and absorption of carbohydrate may lead to carbohydrate intolerance in patients of all age groups. Alteration may occur in the

form of primary inborn defect of absorptive ability involving lactose, sucrose etc due to deficiency of particular enzyme responsible for absorption of the sugar.

Secondary carbohydrate intolerance was first recognised at the beginning of this century in infants. A prolonged and severe illness was attributed to the presence of this complication which was alleviated when offending carbohydrate i.e. lactose was eliminated from the diet. It is known that secondary lactose intolerance is associated with any one of the several systemic and intestinal disorders.

Malabsorption of lactose is a problem of special importance for 2 reasons.

1. The sugar is the major carbohydrate in milk.
2. The intestinal lactose is the most sensitive of all the intestinal disaccharidases to be affected by intestinal infection.

Therefore, lactose malabsorption is one of the most sensitive indicators of mild intestinal insult. Sugar malabsorption also aggrevate the bacterial overgrowth.

Pathological stress like hypoxia can also lead to similar condition.

There are various types of lactose intolerances.

1. <u>Familial lactose intolerance</u>

This is rare but severe disorder characterized by onset of vomiting after the initial feeding of milk.

Intestinal lactose activity is normal. No enzymatic defect has been described.

2. Congenital lactose intolerance

It is characterized by severe diarrhoea, abdominal pain and distension of abdomen soon after birth when the diet begins to contain lactose. The symptoms disappear if milk is replaced by a "clear liquid diet". A lactose free diet is effective treatment.

3. Late onset lactose intolerance

Disorder may appear gradually, begins several years after birth.

Congenital absence of lactase enzyme has been reported in very few cases. The usual mechanism for primary lactose intolerance relates to the developmental patterns of lactase activity, because lactase activity rises relatively late in fetal life and begins to fall after age of 3 years, intolerance can be anticipated in very premature infants and in older children and adults. Late decrease in lactase activity in childhood is common in black and orientals, less common in white. Since lactase activity in the mucosa is at best marginal, this enzyme is particularly likely to be depleted secondary to diffuse mucosal injury.

4. Secondary lactose intolerance

Various causes of secondary lactose intolerance are as follows :

1. Infection.
2. Protein energy malnutrition.
3. Prolonged use of antibiotics.
4. Cystic fibrosis.
5. Cow's milk allergy.
6. Some chronic systemic disorders.
7. Liver diseases.
8. Diseases of pancreas.
9. Immune deficiency disorders.

There are various methods for diagnosing the condition :-

1. Demonstration of reducing substances in stool.
2. pH of stool.
3. Hydrogen breath test.
4. Oral lactosr loading test.
5. Jejunal biopsy.
6. Stool chromatography for detecting the offending sugar.

The purpose of this study was to find out the prevalence of lactose intolerance in chronic diarrhoeal cases and comparative evaluation of efficacy of soya based lactose free formula in lactose intolerance patients and to assess the role of antibiotics treating intestinal infection in cases of secondary lactose intolerance.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

According to Bhan and Bhandari (1989) persistent diarrhoea is an important problem among children during the first two years of life. They observed that the incidence of chronic diarrhoea was 6.3% per year among those aged 0-71 months and highest incidence 31% per year among those aged 0-11 months. There was no significant sex related difference in the incidence of disease. They also observed that there was similar seasonal distribution between acute and chronic diarrhoea. 3-20% of acute diarrhoeal episodes in children in developing countries are persistent (Bhan, 1993).

According to Huttly et al (1989), highest incidence of persistent diarrhoea was among children under 6 months of age. Bhan et al (1989) and Ebrahim et al (1990) also stated that mean age of persistent diarrhoea was between 8-9 months.

In a recent study, Deivanayagam et al (1993) reported that the mean age of children with persistent diarrhoea under 2 years of age was 8.5 months.

Diarrhoea in childhood may be accompanied by secondary alterations in the intestinal mucosa and some deficiencies in the disaccharidase activities. The ingestion of disaccharide during any stage of illness may lead to increased severity of diarrhoea, acidosis and carbohydrate intolerance which improves on elimination of the offending carbohydrate from diet.

Carbohydrate intolerance may be defined as the development of symptoms after the ingestion of carbohydrate either in specific foods or as a specific tolerance test. The symptoms are the result of inadequate digestion and absorption of the sugar. Intolerance may be judged positive when (1) Diarrhoea is induced by feeds containing the offending sugar, (2) Stool pH is below 6, (3) Stool contains more than 0.5% of reducing agent(Lofshotz, 1910).

The developments that have led to an increased understanding and interest in disorders of disaccharide digestion and in disaccharidase deficiencies have come from laboratories involved in both basic sciences and clinical investigations.

About eighty years ago, Finbelstein and Meyer (1910) advocated the feeding of milk with high protein content "EIWSESSMILCH" to infant with gastro-intestinal disturbances. These authors believed that the protein was the substance responsible for the gastro-intestinal disturbances. Later they stated that not only a reduction of whey protein in milk was necessary but also a reduction in milk sugars was required for a complete remission of diarrhoea.

The use and abuse of carbohydrate in infant feeding was discussed by Grulee et al (1912) and Ostheimer et al (1912).

Howland (1921) described congenital intolerance to carbohydrate and temporary intolerance following

diarrhoea. He advocated removal of carbohydrates from the diet of children with prolonged or severe diarrhoea. Renewed interest in diarrhoeal syndromes, associated with maldigestion of specific disaccharides, arose at several pediatric centres. Holzel, Schwartz and Sutcliffe (1959) and Weigers (1962) proposed that a secondary disaccharidase deficiency would be encountered in association with any process which damaged the intestinal cells, such as active or chronic enteritis.

In 1960, Heworth and Ford demonstrated th lack of elevation in blood sugar following ingestion of lactose in patients with gastroenteritis. The fact that intestinal disaccharidases were concentrated in the small intestinal mucosa and more specifically in the microvilli was emphasized by Dahliquist (1960).

Durand et al (1961) used chromatography to demonstrate sugar in stools. They observed that if there was an absolute deficiency of lactose, only then lactose was found in stool while if enzyme deficiency was partial, the respective monohydrates were also found.

In 1962 Giardet described oral lactose tolerance test. Bowce et al (1963) emphasized that the activity of intestinal enzymes was depressed in some acute diarrhoeas. They suggested that high protein diet could, in part, compensate for the decrease in dietetic carbohydrate absorption. They noted that changing from milk to carbohydrate free diet resulted in a dramatic decrease

in stool weight, in 69% patients.

Malcolm et al (1965) suggested that the finding of large amounts of sugar and lactic acid in the stool was due to fermentation of sugar.

Michael et al (1966) reported that lactose activity was lower than maltose or sucrose activity and was the most vulnerable end last to recover. Law and Neole (1966) studied radiographic changes in lactose malabsorption. They found characteristic changes. The small intestine appeared distended by dilute contrast medium, peristalsis was very active, the contrast medium reached the transverse or descending colon within 1 hour while the Haustral pattern was strikingly prominent. Changes of pneumatosis intestinalis may be seen in very severe cases.

The next development that expanded the understanding of disordered disaccharide digestion was the availability of peroral biopsy method that coult easily and safely provide jejunal mucosal tissue for assay of disaccharidase activities. This was regarded as the most reliable diagnostic means. The technique, difficulties, fallacies and limitations were discussed by Anderson (1966) One such limitations was that only a tiny fragment of intestinal mucosa would be examined and that could provide misleading information particularly in disaccharidase deficiency secondary to disease of small gut, with patchy lesions.

Enzyme activity is expressed in units per gram of protein. Each unit splits 1 micromole of substance per minute. Burke (1966) gave the normal range of disaccharidase activity in jejunal mucosa in children as follows :

	Lactase	Sucrose	Isomaltase	Maltase
Range	14 - 132	32-228	31 - 177	83 - 615
Mean	49	95	89	260

Dahlqrist (1966) described a single step ultra-micro method for the assay of intestinal disaccharidases which was most suitable for small quantities of mucosa removed by the peroral biopsy method.

Cochet et al (1981) introduced the breath hydrogen test for children with lactose intolerance.

Majority of the carbohydrate malabsorption syndrome are related to alterations in the function integrity of intestinal mucosa, and its epithelial cells. Additional intolerance to carbohydrates particularly lactose could be due to other etiologies. Generally 3 classes of intolerance types are recognised (Norbert, 1980).

(1) Ontogenic lactase deficiency, also called the physiological deficiency. In this condition the person has either not developed the enzyme or else has lost most of the enzymes function. It could, thus, be seen in premature babies and adults or older children (Cook, 1967). The lactose enzyme develops immediately before birth and

aroundthe age of 3 years, it declines to about 10% of its peak values. This decline, increasing with age, takes place in the majority of ethnic groups who consume very little milk. Northern Europeans, Americans, Mongols and the Tusi falani, Nasi Tribes of Africa maintain high levels of lactase throughout adulthood (Delmont 1968).

At birth jejunal lactase is high in all ethnic groups, irrespective of the status of the enzyme in the adult. In a population where adult hypolactasia prevails fall in the lactase levels takes place in the first 3-5 years of life. In some cases, an early fall, in the first 6-12 months, has been recorded that doubtless accounts for many cases of marasmus (Schrieber et al, 1973). Authors opined that lactase from the breast milk does not get absorbed and that leads to significant energy loss for the infant.

Zambian population have almost a 100% incidence of adult hypolactesia, and infant diarrhoea during breast feeding is common. After the weaning diarrhoea is reported to stop (King, 1960).

(2) Primary Lactase deficiency - First described by Holzel (1967) and his associates. Primary or congenital lactase deficiency is very rare. Only a few reports of its incidence in the western world are available and incidence in India is unknown. Most physicians, however, agree that its incidence is less than one in one thousand. Primary deficiency usually becomes manifest very early in life., though it may have a late onset in adults. Patients have a virtual absence of hydrolytic capacity towards lactase.

but no other abnormality of intestinal structure or function. The precise biochemical defect responsible for the absence of enzymatic activity has not been characterised. The deficiency may be associated with a complete depletion of enzyme protein or with the presence of an abnormal biologically inactive enzyme molecule. The mode of inheritance of this abnormality has not been clarified. Males are at greater risk (Mcnair, 1972).

(3) Secondary lactase deficiency - Damage to the brush border of the enterocytes and loss of mucosal integrity leads to secondary lactase deficiency. A wide variety of agents are known to cause specific damage to the lactase enzyme while diverse systemic and gastrointestinal disordwrs are known to damage villi primarily, leading to reduction of lactase levels. Severe or total villi damage leads to deficiency of all disaccharidases and monosaccharide transport mechanisms (Lindenbaum, 1975).

Lactase is the most superficial of the intestinal oligosaccharidases. Its activity is the rate limiting step for absorption and its concentration is lower than that of other disaccharidases. While decrease in the lactase levels is the main cause of secondary deficiency, other factors such as changes in motility or reduction in absorption surface reduces the exposure time of disaccharides to mucosal enzymes (Ferguson, 1976). Further the author adds that inflammation or anatomical disturbances

could also interfere with enzyme substrate binding, reducing the rate of hydrolytic action to produce a syndrome very similar to secondary deficiency.

Secondary lactase deficiency is thus caused by many factors, the most important of which are mentioned below :

Viral : (1) Rotavirus, (2) Norwalk like agent, Norwalk (3) Non-specific virus, (2) Measles virus (5) Hepatitis virus.

Bacteria : Streptococci, shigella, staphylococci, E.coli, Klebsiella, Pseudomonas.

Mycobacteria : Mycobacterium toberculosis.

Protozoa : Amoeba, giardia (Quinter, 1980).

Candida : it has been associated with chronic diarrhoea and subsequent lactose deficiency (Kane, 1976).

1) Rotavirus Infection

Rota virus infection is a common case of secondary lactase deficiency and since it occurs in young infants it is a major cause of infant diarrhoea (Flewett, 1976). Viral infection may causes varying degrees of structural changes, ranging from spotty subtotal atrophy to severe flattening of villi and derangement of surface epithelium (Hamilton, 1976).

According to Gall (1978) virus invades the mature cells which have high levels of lactase, consequently immature cells from the crypts migrate towards the tip to take the place of damaged cells. The immature cells

tips are lactase deficient, thus leading to intestinal lactase deficiency and diarrhoea.

Systemic viral infections can also cause secondary hypolactasia and malabsorption (Conard, 1978). Hyam's et al (1981) reported that lactose intolerance develops in 50% of cases with Rotavirus infection. Karabocuoglu et al (1994) noticed in their study that rotavirus is known to be the most frequent condition leading to lactase intolerance.

2) Protozoa

The precise cause of malabsorption caused by amoebiasis or giardiasis is not known though a few factors are believed to be involved (Das, 1979). They are : bacterial colonization of the upper small bowel, parasitic injury to mucosa and tissue invasion, mechanical barriers to absorption and bacterial overgrowth with subsequent bile salt deconjugation.

In patients with giardiasis with secondary lactase intolerance , symptoms msy subside immediately after elimination of the parasite (Terruzzi, 1980).

3) Bacteria

Majority of the intestinal bacteria cause damage to the brush border and may produce secondary deficiency. In bacterial diarrhoeas, the malnutrition - gastroenteritis cycle is of great importance since malnutrition predisposes an individual to infection (Chandra, 1982).

Bhan and Bhandari et al (1989) observed enteric pathogens during initial illness in 46.4% of persistent and 55.4% of acute episodes. They reported that the pathogens isolated during persistent episodes include enterotoxigenic E.Coli 9.3%, Salmonellae species 4.7%, Campylobacter 4.7%, Shigella 2.3%, Entamoeba histolytica 2.3% and Rotavirus 2.3%.

Multiple pathogens were isolated in 7% of persistent diarrhoea. E. coli that manifested aggregate adherence was more common 34.9% and it was significantly associated with persistent diarrhoeal episodes. They further identified several risk factors for persistent diarrhoea viz (1) Malnutrition (2) Age $<$1 years (3) Impaired nutritional status, (4) Introduction of animal milk in diet (5) Occurrence of recent diarrhoeal episodes.

Sazawal et al (1992) reported that a much higher risk of persistent diarrhoea with liquid animal milk than spray dried infant formula when compared to breast feeding.

According to Thapa (1994) etiological agents isolated from stool culture in their study were E. coli 18%, Klebsiella 9%, Shigella species 6%, Salmonella 2%, Cholera mitschikom 1%, Giardia lamblia 6% and E. histolytica 1%.

4) Malabsorption syndrome

Individuals living in the tropics may show non-specific villous damage due to diet, environmental pathogens, nutritional status etc. Such non-specific villus damage can cause malabsorption of all foods including carbohydrate (Gray, 1982).

5) Hypoxia

Lifshitz et al (1982) have demonstrated, in rats, that hypoxia could cause long lasting depression of lactase activity. Neonatal hypoxia and respiratory distress have also shown to cause lactase deficiency.

6) Surgical resection of small intestine leads to lactase deficiency (Gudmen, 1983).

7) Cow's milk intolerance

Smith et al (1984) have demonstrated that the incidence of lactase intolerance with milk protein intolerance was as high as 92%. They have suggested that allergic reaction in the intestine led to mucosal damage and depletion of lactase.

8) Helminthic infection

Anchylostomiasis, strongyloidiasis are associated with lactase intolerance (Tandon, 1976).

Development of Disaccharidase activity

Maltase, sucrase and isomaltase in the fetus reached the lower range of normal adult levels by 28-37 weeks of gestation. In both the pre-term and the full term infants their digestion is adequate. In contrast the major digestive enzyme lactase is present at a low level of activity at 28 weeks and then at term the lactase level doubles or triples and reaches adult levels. Theoretically premature infants may be milk intolerant for a few

days until their lactase levels reach adequate levels to digest lactose in their milk formula (Stanley, 1950).

Newborn infants nursed on breast milk which contains 7% lactose are said to have several soft acid stools per day, whereas those fed on Cow's milk formulas containing 4% lactase have only one or two alkaline stools. This is presumably due to relative lactose intolerance (Kistlwr, 1956).

A post weaning decrease in lactase activity occurs in most animal species. Experimentally this decrease can be prevented for several additional weeks if lactose is provided as the only source of carbohydrate (Perkin, 1960).

Contrary to the concept that the intestinal disaccharidases are secreted into the succus entericus, digestion of disaccharides occurs intracellularly. This was first shown by Cejori (1962). It appears that all the enzyme activities are highest in the distal part of the villi and epithelial cells are regenerated in the bottom of the crypts and migrate up the sides of the villi and the highest enzyme activity is obtained at the tips of the villi. Galactosidase or lactase activity has been localised in the microsomes by Doell and Kretchmer (1962) while Dehlqrist and Brun (1962) associated their activity with cytoplasmic granules.

Disaccharidase distribution along the small intestine

Enzyme assays in mucosal specimens obtained by peroral intestinal biopsy indicate that sucrase, isomaltase and lactase are less active in the first part than in the remainder of duodenum. In the upper jejunum and the last segments of the ileum,, the disaccharidase activity is of the same order and magnitude (Hansen, 1963).

Sugar Transport

Assuming that the disaccharidase splitting enzymes are intracellular, the means by which sugars enter the mucosal cells is obscure. This could be by diffusion, if for instance rapid hydrolysis of the disaccharide within the cell maintained a gradient between it and the intraluminal medium. For glucose and galactose, there also exists an active carrier system (Sinclair, 1963).

A further essential requisite is the presence of sodium ions on the membrane of the mucosal cell. The f driving force is regarded, as a form of biological pump, with adenosine triphosphate (ATP) providing the immediate energy source (Burgess, 1964).

Littmann and Hammond (1965) have proposed that sugars enter the intestinal cell by means of a tertiary sugar- sodium carrier complex. This carrier would possess two specific binding sites, one for the substrate and one for sodium ion. The rate of sugar transport seems to be dependent on the difference between intra and extra-cellular

sodium concentration and is also mediated by ATP dependent pump.

The probable mechanisms by which diarrhoeal disease leads to malabsorption can be classified as (Twinly, 1966).

A. Intraluminal events which includes
   - Bacterial over growth
   - Competition
   - Fermentation
   - Cross production
   - Osmotic effects.

B. Cellular events
   - Pharmacotoxic
   - Cytotoxic

C. Villous abnormalities

A. Intraluminal events

Malabsorption could occur because of events in the lumen which interfere with normal digestive and absorptive process. Due to the bacterial overgrowth the bacterial mass competes with the host for the intake of ingested nutrients (Donaldson, 1967).

The effects of bacterial metabolism of ingested nutrients are important. Bacterial fermentation of sugars occur with the production of gas and short chain fatty acids, both of which are capable of producing gastro-intestinal symptoms and increased water loss. Failure to digest and absorb sugars can also result in an osmotic

load in the gastro-intestinal tract and contribute to diarrhoea with secondary effects on vitamin and micro nutrient absorption. Finally, the correlation between carbohydrate malabsorption and bacterial counts in the intestine suggest that carbohydrate malabsorption may contribute to, as well as result from bacterial contamination of the gut (Lifshitz, 1972).

It is especially important to look for E. coli strains in the upper gut. E. coli have been isolated in several cases of lactose intolerance (Cufford, 1973).

Clinical lactose intolerance is an uncommon complication of bacterial dysentery indicating that these infections may be more damaging to colon than to the small intestine (Harry, 1975).

B. Cellular events

The second major category of pathoegenesis relates to the intestinal epithelium and its response to toxins from the lumen of the small intestine. These toxins can be divided into two groups.

i) Pharmacotoxic agents

Studies of xylose and folic acid malabsorption were done by Lindenbaum (1975) in patients with cholera and other related diarrhoeal diseases. He documented that there is a finite period of malabsorption which may be associated with diarrhoea.

Current evidences however indicates that pharma-

cotoxins such as cholera enterotoxin do not affect the intestinal absorption of sugars and amino acids(Rosenberg, 1978).

ii) Cytotoxic agents

They produced damage with or without invasion of mucosa. Shigella toxin contribute to a cytotoxic effect which interrupts normal intestinal epithelial processes, resulting in defects in intestinal malabsorption. Acute intestinal infection from a variety of cases may be associated with morphological and even villous abnormalities of the intestinal mucosa similar to those associated with more severe chronic forms of malabsorption. There is often a loss of absorbing surface (Ostheimer, 1978).

Drugs

Oral contraceptives are known to depress mucosal lactase though the implication of the observations is not clear, as far as children on breast milk are concerned. Neomycin commonly used for control of diarrhoea has been associated with secondary lactase deficiency. It is believed that this is either a direct effect of the drug or it could be due to antibiotic induced enteropathy (Kistler, 1980).

C. Villous abnormalities

The major disaccharidases are located in the microvilli of the small intestinal mucosa and if the

microvilli are damaged, there is usually a resultant decrease in the activity of all disaccharidases. Lactase activity which is lower than maltose or sucrose is most vulnerable and last to recover. Decrease in jejunal maximal absorptive capacity may be caused by loss of digestive absorptive cell mass, by permeability disturbances (external or internal), owing to defective hydrolytic and transport mechanisms or as a result of inhibition of brush border function (Rivera, 1980).

The general pattern of rotavirus infection involves virus penetration and infection of the differentiated enterocytes in the villix of small intestine. Rotavirus multiplies in the cytoplasm of these cells and causes damage to the digestive and absorptive functions (Marykobestes, 1980).

Sequence of events in the small intestine consist of replacemrnt of the absorptive villous epithelial columner cells with cuboidal cells and shortening of villi with lymphocyte infiltration. Available evidence suggests that such damaged cells are sloughed into small intestine. Lysis of the infected cells release virus into the intestine. These studies suggest that diarrhoeas caused by rota virus infection is due to malabsorption which also includes impaired carbohydrate absorption. The highly differentiated absorptive villous cells are replaced by immature crypt cells that are not able to compensate for absorption defect (Yates, 1980).

Such changes occur in a cephalo-caudal direction and suggests that much of the diarrhoea is due to loss of absorptive capacity. Histological abnormalities have ranged from mild flattening of the mucosa to complete mucosal atrophy. A decrease in the rate of intestinal dell turnover and decrease in the mitotic index have been noted. Enzyme studies after about 3 weeks of treatment show that the defects in the absorption of monosaccharides and hydrolysis of disaccharides (sucrose, maltose) tend to disappear. However, there is both histochemical and clinical laboratory evidence that the defect in lactose metabolism is the last to get corrected (Leichberg, 1980).

In cases of malnutrition where the gut is previously damaged, gastrointestinal infection or infestation may be a factor in producing an acquired disaccharide intolerance (Valman, 1980).

Normal lactase activity in the jejunum requires more protein than what is necessary for maltase activity. So it will be more easily influenced by the combined effect s of malnutrition and gastrointestinal infections. As soon as the inciting cause of mucosal damage subsides, as in acute gastroenteritis, enzyme activity increases. Although lactose tests may become normal, lactase levels remains abnormally low for years. The continued ingestion of lactose may aggravate the acute gastroenteritis (Barnes, 1982).

The excess of volatile organic acids especially acetic and lactic acid produced by bacterial fermentation irritate the intestine, which induce peristalsis and excretion of fluid and mucous. Thus, absorption is disturbed with subsequent diarrhoea. Once diarrhoea is present mono-saccharides are also poorly absorbed(Naser, 1983).

Diagnosis of carbohydrate intolerance is suspected at a time when in the history of a diarrhoeal episode there are increasing number of motions and consequent dehydration. The stool are watery, frothy and explosive, accompanied by irritability, abdominal distension and perianal soreness with high stool weight (Lifshitz et al, 1980).

In carbohydrate intolerance (due to lactase deficiency) significant improvement of symptoms occur and a decrease in the stool weight occurs on withdrawal of milk from the diet. Diarrhoea recurs on reintroduction of milk to the diet. Withdrawal of milk from diet decreases the stool weight by 69% (Bowie et al, 1981).

The finding of abnormally large amounts of lactic acid and sugar in the stool while on milk suggests that there is fermentative diarrhoea (Harker, 1981).

Fermentative diarrhoea may be due to malabsorption of mono, di, or polysaccharides. The unabsorbed carbohydrate is subjected to bacterial action which produces organic acid in large quantities as an end product (Weijer, 1982).

Bowie and Brinkman (1981), Ghait et al (1982) and Harry et al (1983) demonstrated the association of disaccharide intolerance and protein calorie malnutrition.

TABLE : Showing percentage cases of carbohydrate intolerance in different studies(Ashoka, 1988).

Sl. No.	Author	Year	Percentage
1.	Chandra R. K.	1968	54.0
2.	Reddy	1972	37.0
3.	Udani, P.M.	1976	9.32
4.	Archer	1977	12.0
5.	Ansari	1976	10.0
6.	Hirschorn	1980	50.0
7.	Ghai, O.P.	1982	23.0
8.	Bhave	1983	37.0
9.	Clifford	1983	12.0
10.	Davidson	1984	50.0
11.	Trounce	1985	10.9

Clinical consequences of lactose intolerance

1. Prolongation of diarrhoea : Average duration of rota virus diarrhoea, is 5-7 days. It may get prolonged to 10-14 days due to lactose intolerance according to Hyams and Krause (1970).

2. Metabolic acidosis : Lactose on fermentation yields lactics acid which is absorbed partially and may stimulate bicarbonate secretion (Rivera et al, 1972).

orally and blood sugar estimated at 15, 30, 60, 90, 120 minutes. If the lactose level was low, blood glucose rise and less than 1.1 m mol/l

3) Presence of reducing substances in the stool

Diagnosis of carbohydrate intolerance could be made with Benedict's reagent when reducing substances such as lactose, glucose and galactose are excreted in stools in concentration above 0.25%. The presence of reducing substances could be determined by a change in the colour of diluted fresh stool sample (Joseph, 1976).

In case of sucrose, preliminary hydrolysis using HCl was done so as to split sucrose into glucose and fructose (Vincent, 1979).

Estimation of stool reducing agents was unreliable techniques in the diagnosis of lactose intolerance as opined by Rossi (1990).

4. Rubner's test

This test has been used to detect reducing substances in the stool.

According to Singh et al (1985) incidence of false positive tests was considerably reduced in Rubner's method as compared to the conventional benedict's test. To the liquid stool sample lead acetate was added and boiled cooled and then 2 ml of liquid ammonia was added. A pink or red precipitate showed lactose in the stool.

3. Malnutrition : Carbohydrates form the major source of energy especially in the infant. Since 50% of the calorie requirements are derived from lactose, loss of the sugar to the system leads to caloric defects, even when the diarrhoea is mild.

Presence of unabsorbed carbohydrate in the lumen also enhances protein and nitrogen loss. Unhydrolysed carbohydrate also interferes with fat malabsorption due to dilution of bile salts (Mcnair, 1972).

4. Bacterial proliferation : The presence of unabsorbed carbohydrates and fermentation products in the small bowel lumen and proliferation of enteric bacteria in the upper segment of intestine. Such overgrowth of faecal flora in the upper segment of small intestine leads to a state of chronic diarrhoea. Altered motility, presence of free carbohydrate in the lumen, and other metabolic alterations (luminal pH) are among other factors that influence enteric bacterial dissemination. Bacterial over-population of the upper bowel may generate additional injurious factors such as deconjugated bile salts, hydroxy fatty acids which aggravate intestinal malfunction and worsen diarrhoea (Berr, 1981).

5. Pneumatosis intestinalis may result from carbohydrate intolerance since unabsorbed carbohydrates generate large quantities of gas in the intestinal lumen, which

if not expelled may lead to distension of gut with increasing pressure, leading to ischemia or necrosis of the intestinal mucosa. Thus, providing access for the gas into the tissue spaces and resulting in pneumatosis intestinalis (Vazquez and Amador, 1983).

6. Macromolecular absorption : An increased macromolecular absorption occurs resulting into development of hypersensitivity and allergy to food stuffs. Experimentally it is proved that elevated luminal osmolarity leads to enhanced rate of transport of macromolecular traces across the intestinal epithelium (Teichbergs, 1985).

EPITHELIAL AND BASEMENT MEMBRANE ABNORMALITIES

Goulet Oliver et al (1995) studied 6 children with watery diarrhoea in the neonatal period requiring total parenteral nutrition. Repeated duodenal and jejunal biopsies had revealed villious atrophy with normal or hyperplastic and regenerative cryptae, normal cellularity of lamina messenteri propria and no signs of T cell activation. The main histological features observed by them were epithelial dysplasia with focal crowding and disorganisation of surface enterocyte, pseudocystic formation of glands abnormal regenerative cryptae.

The basement membrane component were studied with polyclonal antibodies on frozen specimen and were compared with biopsy specimen from patients with coelic disease, or

autoimmune enteropathy. Relative to control subjects there was faint and irregular deposition of lamina at the epithelial lamina mesentrii propria interface, whereas deposits of heparin sulphate proteoglycan were large and lamellar.

Primary and secondary nature of their modifications of basement membrane remains to be determined, but the modifications might be related to epithelial abnormalities and to the severity of this neonatal diarrhoea which resisted all treatment and required permanent total parenteral nutrition.

INVESTIGATIONS IN CARBOHYDRATE INTOLERANCE

1. Stool pH

Stool pH was first suggested by Davidson in 1967. Opinions vary remarkably on the reliability of stool pH in the diagnosis of lactose intolerance.

Measurement of stool pH in lactose intolerance is unreliable, full of fallacies and subject to wide fluctuations according to Martino and Lifshitz (1960). On the other hand Durand (1960) stated that measurement of stool pH was reliable and stool pH was less than 6 in all cases of lactose intolerance.

2. Oral lactose loading test

In 1962, Giardet described oral lactose loading tests, after taking a fasting blood sugar sample. Fifty grams of lactose dissolved in 400 ml of water was given

5. Stool chromatography

It is one of early techniques used in diagnosing cases of carbohydrate intolerance and it continues to be one of the most specific and reliable methods.

Durand et al (1961) used paper chromatography for the first time to identify offedning carbohydrate in stool.

Separation and identification of different sugars becomes clear by thin layer chromatography as opined by Joseph (1974).

Thin layer chromatography can pin point the exact offending sugar. It is extremely useful in the diagnosis of monosaccharide malabsorption where there are rapid changes in the type of food given as observed by Udani (1976).

Bhave et al (1983) observed that stool chromatography was extremely reliable in the diagnosis of lactose intolerance though it was painstaking and time consuming method.

Karabocuoglu et al (1994) reported that thin layer chromatography when done in conjunction with fecal pH determination and clinitest tablet assay method was suggested as a useful method in confirming and supplementing the results of these tests.

6. Clinitest method

In 1964 Kerry and Anderson developed a new and easy method for the diagnosis of sugar in stool. TO 15 ml of stool suspension an indicator tablet was added and a

chemical reaction similar to that of urine was seen. This test was not intended to provide conclusive evidence of defective carbohydrate digestion, but indicated that patient could be investigated for sugar malabsorption more intensively.

7. Jejunal biopsy

Quantitative, biochemical assay of disaccharides in per oral biopsy of intestinal mucosal specimen is regarded as one of the most reliable diagnostic means.

Direct estimation of lactase concentration and the morphology of the biopsy specimen give the idea of the type of hypolactasia. In specific primary hypolactasia the villi are basically normal, together with other disaccharidase concentration (Reddy, 1975).

Small bowel biopsy according to Byrne (1981) is not justified in the diagnosis of carbohydrate intolerance. Since it can be diagnosed better by other non-invasive technique.

8. Breath hydrogen test

Cochet et al (1981) introduced the breath hydrogen test for children with lactose 1 gm/kg as syrup was given orally. Expired breath samples were collected at 0, 60, 90 minutes and analysed for hydrogen concentration. An increase in breath hydrogen, more than 20 parts per million was considered as positive result.

Unabsorbed lactose on fermentation liberates hydrogen and carbondioxide. These gases are finally eliminated through the breath. This technique has the advantage of being non-invasive (Moffei et al, 1982).

According to Bufford et al (1982) breath hydrogen test permits the study of intestinal malabsorption of disaccharidase activity after diarrhoea and may help in deciding the re-introducing of certain carbohydrates into the diet.

Solomon et al (1983) have pointed out that there may be lower hydrogen production in some patients with severe diarrhoea and carbohydrate malabsorption because the frequency of bowel movements may wash out the colonic bacteria, thus giving false negative results in hydrogen breath test.

9. Radiography in Carbohydrate intolerance

Law and Neale (1966) described radiological changes in disaccharidase deficiency.

TREATMENT

Malcolm et al (1965) advocated the practice of withholding milk in protracted diarrhoea.

Opinion differs as to when milk diet should be restarted. According to Jeffrey et al (1974) it could be started after 10-14 days while Davidson et al (1978) advised a period of atleast 4 weeks.

According to Shub and Walker (1980) oral feeding should be started as early as possible at least partially The author opines that enteric feedings have a trophic effect on the hypoplastic or damaged intestinal mucosa facilitating early healing and inducing a more rapid return of disaccharidases.

Soyabeen preparations were suggested as a milk substitute by Hill and Stuart (1980).

Larcher et al (1980), Bhan et al (1983) and Bhave et al (1983) have emphasized that there may be intolerance to low lactose formulae due to associated milk protein intolerance and gluten sensitivity. To cope with such situations, authors have devised some diets prepared from locally available ingredients.

In 1984 Bedline and Boylis suggested that one substrate like glucose could reverse the net secretion and the associated clinical symptoms induced by malabsorption of another substance like lactose.

Larcher et al (1984) have made it clear from numerous animal and human studies, that intraluminal food stuffs, carbohydrates and proteins increase intestinal digestive enzyme and cell proliferation in a dose related way. The inductions are somewhat specific. Sucrose induces sucrase formation. Therefore, a mixed carbohydrate diet was most protective against disaccharidase depletion, during diarrhoea.

Mabel et al (1984) has demonstrated that resumption of milk feeding is associated with prompt improvement in nitrogen balance.

Walker et al (1985) postulated that disaccharidases are continuously being synthesised and degraded in the epithelial cells of the small intestine. Decrease in disaccharidases could be explained by either a decline in the rate of synthesis of new enzyme or an increase in the rate of degradation.

A study conducted by Davidson (1984) revealed that antibiotics do not influence the development of either biochemical or chemical malabsorption of lactose.

Brunser and Arya et al (1990) has to be refed with low lactose products to induce remission of the symptoms. They obserbed that nutritional parameters were unchanged during and after the diarrhoeal episodes. Their findings suggested that availability of low lactose formula may be advantageous in clinical management of infant with acute diarrhoea and evidence of lactose intolerance.

Bean and Fontaine et al (1990) suggested that formula based on fermented milk together with oral rehydration can be used to treat malnourished children with sugar intolerance diarrhoea. They observed no difference in mean weight gain between children with sugar intolerance malnourished children and other chronic/acute diarrhoeal cases which had not shown the sugar intolerance.

Sinden and Sutphen (1991) observed that in lactose intolerance children were successfully treated with infant formula, including soya protein and hydrolysate formula in secondary lactase difficiency. He also observed that diet supplemented with lactose can be beneficial in lactose intolerance diarrhoeal patients. The ingestion of milk with food and fibre components in diet had also been shown to improve symptoms of lactose intolerance.

Businco et al (1992) observed that soya based milk was used for different conditions including cow milk protein allergy and lactose intolerance. Feeding soya protein formula to normal term infants is associated with normal growth, normal protein nutritional status and normal bone mineralization. Recent studies of infants fed soya protein formula revealed no immunological abnormalities. He observed that children fed on soya milk protein had allergy with soya protein formula.

A recent Indian study (Bhan and Bhatnagar et al (1992) found no improvement in purge rate, weight gain or overall illness among children with persistent diarrhoea treated with oral gentamycin than with a placebo.

Overall 5% of hospital referred patients required intravenous therapy for few days before full oral feeding is possible. Remaining 80-90% recovered on initial diet and 10% required change of milk free diet. Although the role of antibiotics is achieving recovery from persistent diarrhoea has not been substantiated, systemic antibiotics

may be required in nearly one third of hospitalised persistent diarrhoea cases for associated pneumonia, urinary tract infection or bacteremia as is true for any group of sevmrely malnourished hospitalised cases (Bhan and Bhatnagar, 1993).

Gupta and Gupta et al (1993) observed that soya based milk formula was commonly prescribed for lactose intolerance secondary to infective diarrhoea. They studied two groups of cases, first group of seventy patients was given lactose predigested milk feeding and the second group was treated with soya milk. They observed that refusal of feed was found 30% cases with soya based milk as compared to only 2.8% in lactose predigested milk (lactose group). Vomiting after feed was also found in 10% of babies fed soya based milk as compared to none in lactose group. Motions were controlled in 84.3% cases within 3 days of therapy. They concluded that lactose treated milk was more superior than soya milk for the treatment of lactose intolerance.

Nutritional management plays a vital role in many gastrointestinal problems, most common problem is lactose intolerance. Spollett et al (1994) concluded in their study that lactose free diet was most successful therapy in lactose intolerance diarrhoeal patients.

Thapa et al (1994) studied one hundred twenty infants under one year of age suffering from intractable

diarrhoea. All patients had received prior treatment in the form of antimicrobials and intravenous fluid 33% of cases antimotility agents 50% cases and stool binding substance in 50% cases, 30% need hospitalization. He observed other symptomatology viz. vomiting 44%, dehydration 23%, fever 33%, paralytic ileus 9%, perianal excoriation 47%, and rectal prolapse 3% of cases, anaemia 70%, vitamin deficiencies 10%, and pedal oedema 3% cases. They reported that besides intractable diarrhoea other associated infection were septicemia 22%, bronchopneumonia 6%, meningitis 4%, and urinary tract infection in 3% of infants. Among them 53% of infants had secondary lactose intolerance.

Pitchumoni (1995) stated that one the diagnosis of lactose intolerance was confirmed, simple dietary management may resolve symptoms completely.

Controlled clinical experience with antibiotics therapy is limited. Hill et al (1984) reported beneficial effects with oral gentamycin therapy in persistent diarrhoea. Their strategy allowed selection mainly of cases of severe high purging diarrhoea of more than 5-7 days.

MATERIAL AND METHODS

MATERIAL AND METHODS

The present study was carried out in the department of Paediatrics and department of Biochemistry and Microbiology, M.L.B. Medical College, Jhansi.

SELECTION OF CASES

The cases included in this study comprised of children with chronic diarrhoea. Those who were admitted in Pediatric ward. Persistent diarrhoea and chronic diarrhoea was considered when it lasted for more than 2 weeks.

HISTORY AND CLINICAL EXAMINATION

In each case a detailed history particularly with regard to diarrhoea, its duration and severity, nature of stool, colour of motion, presence of mucous or blood was recorded.

History of vomiting, abdominal distension, crampy abdominal pain, frothy stools, perianal excoration, failure to thrive, fever, anorexia were noted.

Detailed dietary history regarding the nature of feeds, date when artificial milk was started, was noted. Nutritional history regarding the average amount of proteins and calories consumed was assessed.

In the physical examination main stress on whether the child had signs of malnutrition, and dehydration besides a general examination of other system was done.

INVESTIGATIONS

Stool Examination

Gross Examination : Clour, odour, frothiness and presence of mucous or blood were noted.

Microscopic Examination : Stool samples were examined for the presence of ova, cysts, particularly of giardia and Entaboema histolytica, presence of pus cells and red cells were also noted.

Stool Culture : In every case stool culture was done at the time of admission, prior to antibiotic therapy.

Stool pH : Estimation of pH was done in all samples immediately after collection. It was done using sensitive narrow range, D.D.H. paper. pH estimation was done both at the time of admission and also at the time of discharge.

Stool for recuding substances : All the samples within 1 hour of collection were tested for reducing substances by Benedict's test.

To 5 ml of Benedict's reagent, 8 drops of liquid stool was added and boiled for about 2-3 minutes and the colour change, especially the precipitate formed was noted. It ranged from greenish yellow 1+, yellow ++, orange +++ and brick red ++++.

In case where sucrose was suspected as the offending sugar, acid hydrolysis were done. For hydrolysis stool filtrate was boiled with equal amount of N/10 HCl for 30 seconds prior to testing with benedicts' reagent. Presence of sugar in stool 75% was taken as evidence of sugar intolerance.

Rubner's test

All the samples were subjected to Rubner's test which is yet another test for detecting the presence of reducing substance in stool.

1-5 ml of liquid stool was taken in a test tube. To this was added 0.3-0.5 gm of lead acetate. The solution was boiled for -24 min and then cooled. Subsequently, 2-3 ml of strong liquid ammonia was added to agbove solution. It was again boiled for 2-4 min and then allowed to stand 5-10 min. A pink or brick red precipitate showed sugar in stool while yellowish or dirty white precipitate showed negative results. If the test was negative 2-3 ml of strong liquid ammonia solution was again added and the solution was boiled for 2-4 min. After allowing resultant solution to stand for 5-9 min. colour of precipitate was again observed. The last procedure was done according to modified Rubner's test.

Stool Chromatography

Initially the stool sample was prepared by suspending stool in distilled water, centrifuging and then filtering the supernatant. The filtrate was used directly for chromatography.

Ascending thin layer chromatography (TLC) method was employed using silica gel as the medium. Impregnated on glass slide. The solvent used was a mixture of N. Butanol, glacial acetic acid and distilled water, ratio of 60:30:4. The stool sample along with pure stanadard

solution of different sugar like lactose, sucrose, glucose were placed on the silica gel slide using the fine capillary glass tube. Then, the silica gel plate was kept in glass chamber which contained the solvent. By capillary action, the solvent rose on glass plate and in about 6-7 hours solvent the top of plate. The plate was removed and dried in hot air oven at 110°C for about 15 min. The chromatogram was then stained using universal iodine dye. The sugar present in sample was identified by visual comparison of the sample spot with the spot of the standard sugar samples and a qualitative estimation was done (Stahl, 1969).

THERAPY

The care was taken who were positive only lactose on chromatography.

Two groups are prepared on who are treated initially with lactose free formulae milk (soya based) and if stool culture report is positive, appropriate antibiotics are added to the regimen for seven days.

Cases of second group were fed on mother's milk and one of the commonly used antibiotic (Amikacin) for fur infection was started and changed to appropriate antibiotics depending upon culture and sensitivity report. Antibiotics was used for seven days. If there were no improvement at the end of seven days of appropriate antibiotics, treatment of those cases were switched over to treatment same as group first.

O B S E R V A T I O N S

OBSERVATIONS

This study was conducted in the Department of Pediatrics, M.L.B. Medical College, Jhansi. The study material comprised of children admitted in pediatric ward with chronic diarrhoea.

The period of study extended for a period of one year from 10.9.94 to 15.9.95. During this period 85 patients admitted with chronic diarrhoea were studied.

Chromatography was done in Biochemistry Department, M.L.B. Medical College, Jhansi. Cases were considered as positive only when offending lactose was demonstrated by chromatography.

TABLE I : Incidence of lactose intolerance in chronic diarrhoea.

Positivity	No.of cases	Percentage
Sugar positive	45	52.35
Lactose positive	32	
Incidence	71.1%	

It is evident from the table I, out of 85 cases of chronic diarrhoea 45 cases showed sugar positivity in stool as evidenced by chromatography (52.35%). These 45 cases further subjected to chromatography studies it was seen out of 45 cases 32 showed positivity lactose intolerance (71.1%).

TABLE II : Age incidence of children with lactose intolerance.

Age group (months)	No.of cases	Percentage
0 - 3	4	12.50
4 - 6	9	28.05
7 - 12	12	37.50
13 - 18	5	15.70
19 - 24	2	6.25

Table II shows that maximum (37.50%) cases of with lactose intolerance were in the age group of 7-12 months of age. Minimum 2 (6.25%) cases were in the age group of 19-24 months. It was calculated that mean age group of all the lactose intolerance patients was 9 months. Youngest child was 1½ months of age and eldest was 20 months of age.

TABLE III : Sex incidence in lactose intolerance patients.

Sex	No.of cases	Percentage
Males	22	68.75
Females	10	31.25

Table III shows that out of 32 children 22 (68.75%) were males and remaining 10(31.25%) children were females. The male : female ratio was 2.2 : 1.

TABLE IV : Showing the socio-economic status.

Socio-economic status	No.of cases	Percentage
Upper class	1	3.13
Middle class	6	18.75
Lower class	25	78.12

Majority of the cases (78.12%) was from lower socio-economic status. There was only one (3.13%) case from upper class.

TABLE V : Showing the nutritional status according to I.A.P. Classification.

Grade of Nutrition	No.of cases	Percentage
Normal	2	6.25
Grade I malnutrition	6	18.75
Grade II malnutrition	10	31.25
Grade III malnutrition	8	25.00
Grade IV malnutrition	6	18.75

Table V shows nutritional status of the patients. Majority of the cases were suffering either mild grade malnutrition or moderate grade of malnutrition.

TABLE VI : Showing administration of antibiotics prior to admission.

Antibiotic taken	No.of cases	Percentage
Taken	28	87.50
Not taken	4	12.50

Table VI shows that majority (87.50%) of cases came to the hospital with the history of antibiotics administration prior the admission.

TABLE VII : Comparative evaluation of sugar intolerance in patients who had received breast milk alone and artificial milk feed.

Type of feed given	No.of cases	No.of sugar positive cases	Percentage
Breast milk alone	25	14	56.00
Artificial milk alone.	20	7	35.00

Table VII shows that breast milk feeding was the major cause of sugar intolerance, while sugar intolerance with artificial milk was less (35.00%).

The table VIII reveals that majority of children (37.50%) received artificial milk feeds along with breast feed. Artificial feeds consisted of cow's milk and fuffalo's milk.

TABLE VIII : Showing the dietary history of patients.

Type of feeds given	No.of cases	Percentage
Breast milk alone	9	28.12
Breast milk + artificial (Cow's/buffalo's) milk	12	37.50
Artificial milk alone	5	15.62
Milk + semisolids	6	18.75

TABLE IX : Showing symptoms and signs at the time of admission.

Presenting manifestation	No.of cases	Percentage
1. Watery diarrhoea	28	87.50
2. Semisolid consistency	9	28.12
3. Fever	18	56.25
4. Vomiting	14	43.70
5. Abdominal distension	12	37.50
6. Stool frequency :		
<5	-	-
5 - 10	12	37.50
10 - 15	18	56.25
>15	2	6.25
7. Perianal excoriation	24	75.00
8. Signs of vitamin deficiency :		
Vitamin A	2	6.25
Vitamin B	4	12.50
Vitamin C	1	4.13

Table IX shows that 28(87.50%) cases presented with diarrhoea of watery consistency. Almost all of them had fever along with vomiting. Abdominal distension was seen in 12(37.50%) cases. Stoo frequency was more than 10 motions per day in 18(56.25%) cases. Perianal excoriation was seen in 24(75%) cases of chronic diarrhoea with lactose intolerance.

TABLE X : Showing the dehydration score according to WHO(1980).

Degree of hydration	No.of cases	Percentage
Plan A (No dehydration)	9	28.12
Plan B (Some dehydration)	17	53.13
Plan C (Severe dehydration)	6	18.75

Table X shows that out of total 32 cases, 17 (53.13%) cases presented with some dehydration and were in plan B dehydration score according to WHO (1980).

TABLE XI : Showing associated systemic diseases.

Diseases	No.of cases	Percentage
A.R.I.	8	25.00
Encephalitis like disease	3	9.37
Malaria	4	12.50
Severe anaemia	2	6.25

Along with protracted diarrhoea, 17(53.12%)

cases had some or the other systemic illness. Predominantly of respiratory ifections. 4(12.50%) cases were suffering with malaria, 2(6.25%) had severe anaemia.

TABLE XII : Showing the duration of diarrhoea.

Duration (days)	No.of cases	Percentage
14 - 28	27	84.37
7 28	5	15.63

Table XII depicts that 27(84.37%) cases were having chronic diarrhoea with lactose intolerance from 14-28 days. Rest 5 (15.63%) cases were presented with more than 28 days duration of diarrhoea.

TABLE XIII : Showing stool examination.

Stool Examination	No.of cases	Percentage
Physical characteristics	24	75.00
Yellowish	24	75.00
Greenish yellow	8	25.00
Microscopic :		
Round worm	3	9.38
Hook worm	-	-
Amoeba	2	6.25
Giardia	-	-
Pus cells	4	12.50
Fat globules	-	-
Stool culture :		
E. Coli	3	9.38
Shigell	1	3.13

In 75% of cases admitted with protracted diarrhoea the lactose intolerance stool was yellowish and frothy. Pus cells were detected in only 4(12.50%) cases and ova of round worm seen in 3(9.38%) cases. Amoeba were present in 2(6.25%) cases. No giardia and hook worm seen(Table XIII)

Stool culture revealed organisms in only 4(12.50%) cases. The predominant organism was E. Coli in 3 cases and Shigella was found only in 1 case(Table XIII).

TABLE XIV : Showing pH in stool of lactose intolerance children.

Stool pH	No.of cases	Percentage
6.0	8	25.00
5.5	18	56.25
5.0	4	12.50
4.5	2	6.25
TOTAL	32	100.00

At the time of admission, 18(56.25%) cases had stool pH of 5.5. pH of majority of the cases ranged between 5 to 6. The stool pH was 4.5 in only 2(6.25%) cases(Table XIV).

Out of 85 cases presenting with chronic diarrhoea, 51 showed evidence of reducing substance by Benedict's test. Majority of the cases had reducing sugar (0.25 to 1.9 gm%) in stool. Only 10(22.33%) cases had more than 3 gm% of sugar in stool (Table XV).

TABLE XV : Stool reducing substances as detected by Benedict's test.

Colour and precipitate	Range of sugar (gm%)	No.of cases	Percentage
Greenish	0.25-0.90	16	35.50
Yellow	1.00-1.90	16	35.50
Orange	2.00-2.90	9	20.10
Brick red	7 3	10	22.33

TABLE XVI : Stool reducing substances as detected by Rubner's test.

Colour of precipitate	No.of cases	Percentage
Pink (Positive)	48	55.80
White(Negative)	37	44.20

Rubner's test was positive in 48(55.80%) cases whereas it was negative in 37(44.20%) cases.

TABLE XVII : Comparative evaluation of Benedict's and Rubner's tests.

Test	True +ve	True -ve	False +ve	False -ve	Sensitivity	Specificity
Benedict's	45	40	6	3	93.70%	86.90%
Rubner's	45	40	3	4	90.45%	93.02%

On comparative evaluation it was observed that there were 6 false positive cases with Benedict's test

as compared to only 3 cases with Rubner's test, and there were 3 false negative cases with Benedict's as compared to 4 false negative by Rubner's test. Thus it was concluded that Benedict's test was more sensitive (93.7%) as compared to Rubner's test (90.45%), but it was less specific (86.9%) as compared to Rubner's test (93.02%) (Table XVII).

TABLE XVIII : Stool chromatography.

Test	No.of cases	Percentage
Sugar positive	45	52.80
: Single	32	70.90
: Multiple	13	29.10
Sugar Negative	40	47.20

Out of 85 cases, 45 were positive for chromatography. Out of these 45 positive cases, 32(70.9%) cases were single positive for lactose and remaining 13 were multiple positive. 40(47.2%) cases were negative for chromatography.

Table XIX shows that among the various sugars present in the cases, lactose was the predominant. It was seen in chromatography in 32(70.90%) cases whereas multiple sugars were found in 13(29.1%) cases. It was combined with glucose, sucrose and galactose. There was a combination of lactose with glucose in 4(8.80%) cases. The

combination of lactose with sucrose was present in 4.4% cases. While multiple sugars combination of lactose, sucrose and galactose was in 6(13.30%) cases, whereas the combination of lactose, glucose and galactose was in only 1(3.13%) case. No more than three sugars were found in any case.

TABLE XIX : Pattern of sugar tolerance as revealed by chromatography.

Type of sugar	No.of cases	Percentage
Lactose	12	70.90
Lactose and glucose	4	8.80
Lactose and sucrose	2	4.40
Lactose+glucose+galactose	1	3.13
Lactose+sucrose+galactose	6	13.30

According to table XX, out of 32 cases, 18 cases were kept on soya based lactose free formula therapy. 11 (34.4%) cases were kept on antibiotic therapy alone. And three cases were treated with antibiotics plus soya based lactose free formulae, while 5 cases needed additional antiamoebic therapy along with soya based formula and antibiotics. Only 1 case was treated with antifungal plus antibiotics and soya based lactose free formula.

TABLE XX : Treatment given in chronic diarrhoea due to lactose intolerance.

Therapy	No.of cases	Percentage
Soya based lactose free formula alone	18	56.25
Antibiotics alone	11	34.40
Antibiotics + lactose free milk formula	3	9.38
Intravenous fluid therapy	16	50.00
Other therapy		
Antiamoebic+soya based formula + antibiotics	5	15.62
Antifungal + soya based lactose free formula.	1	3.13

TABLE XXI : Response of soya based lactose free formula in days in 18 cases.

Response (days)	No.of cases	Percentage
0 - 5	13	72.30
5 - 7	5	27.70
TOTAL	18	100.00

Table XXI shows the response of soya based lactose free formula therapy. 13(72.30%) cases responded within 5 days of therapy. Not even a single case needed therapy beyond 7 days.

TABLE XXII : Response of antibiotics alone in 11 cases.

Response (days)	No.of cases	Percentage
0 - 5	-	-
5 - 7	4	36.40

Table XII shows that out of 11 cases kept on antibiotics alone only 4 (36.4%) cases were symptoms free within 5-7 days, while 7(63.60%) cases were switched over to soya based lactose free formula after 7 days of therapy as shown in table IV. All of them responded the therapy (lactose free soya based) within 7 days of initiation of soya based lactose free diet. 3 cases responded within 5 days and remaining 4 cases were responded within 5 days of therapy.

TABLE XXIII : Cases switched over to soya based lactose free formula milk.

Response (days)	No.of cases	Percentage
0 - 5	3	42.80
5 - 7	4	57.20
7 7	-	-

The cases which were kept on antibiotic alone, had other systemic diseases also. Only 7 cases not responding to antibiotic therapy were supplemented with

soya based lactose free formula. All of them responded with this therapy within 7 days as shown in table IV.

TABLE XXIV : Antibiotics used in chronic diarrhoea.

Antibiotic used	No.of cases	Perce-ntage	No.of cases responded
Amikacin alone	7	63.60	3
Amikacin+Cefotexim	4	36.40	1

Table XXIV shows that out of 11 cases, 7 (63.60%) cases were treated with amikacine alone. Of these 7 cases only 3 cases responded to therapy. And the other 4 (36.40%) cases were treated with amikacin plus cefotexim. Of these four cases only one case responded the therapy. The organisms (E. Coli and Shigella) were sensitive to amikacin.

The cases which were treated with antifungal and antiamoebic therapy were not included in the study.

D I S C U S S I O N

D I S C U S S I O N

Diarrhoea is one of the most important public health problems and a major cause of death among infants in the developing countries. In vast majority of cases, diarrhoea in infant is self limiting and caused by viral or known pathogens which are idenfied by routine stool culture. In some infants however inspite of the ordinary supportive measures instituted during the diarrhoeal episodes, diarrhoea continues for protracted period. Some of these children are found to have developed intolerance to carbohydrate component of milk at the same time, leading to perpetuation of diarrhoea with its consequences.

According to present study, conducted at the Department of Pediatrics, Microbiology and Biochemistry, M.L.B. Medical College, Jhansi prevalence of carbohydrate intolerance in chronic diarrhoea was 52.35%. Chandra et al (1969) used stool pH estimation along with oral lactose feeding test to diagnose lactose intolerance. Thus, they detected lactose intolerance in 54% of cases.

Reddy et al (1972) used similar methods and detected intolerance in 37% of cases. Udani et al (1976) reported prevalence rate of 9.32%, Larcher et al (1977) using stool pH estimation alongwith estimation of reducing agent content of stool reported a prevalence rate of 24% for carbohydrate intolerance.

Bhave et al (1983) employed stool chromatography and reported a figure of 35.7% prevalence rate. In 1984 Davidson et al used the much acclaimed breath hydrogen test and detected 50% prevalence rate.

Present study which was mainly concerned about prevalence of lactose intolerance in protracted diarrhoea reported in 71.1% of cases (Table I) while 13.3% had lactose in addition to galactose and sucrose. Lactose intolerance was observed in 8.8% cases, while lactose and glucose were seen in 4.4% of cases. Triple sugar viz. lactose, sucrose and galactose was presenr in 16.43% cases.

Bowie et al (1965) studied acquired disaccharide intolerance in malnourished children. Disaccharide ihtolerance was found in 52% of Cases. The predominant sugars detected in their study were lactose, glucose and galactose.

Udani et al (1976) in their study detected lactose in stool in 30% of cases and lactose with other sugars in another 30% of cases. Sucrose alone was seen in 20% of cases and glucose alone in the remaining 20% of cases. The intolerance to maltose and fructose was rare, in their study.

Joseph et al (1976) reported in their study an incidence of 30% of sugar intolerance in refractory diarrhoea, diagnosed by thin layer chromatography . lactose alone was seen in 80% of cases.

Vincent et al (1979) reported an incidence of 59% for sugar intolerance in acute diarrhoea. In 40% of cases it was single sugar intolerance being lactose while in the rest of the cases multiple sugar intolerance viz. glucose, sucrose and galactose was observed.

Ansari et al (1979) reported in their study that lactose was detected by chromatography in all the cases of sugar intolerance. Besides there was intolerance to sucrose and galactose in 40% and 20% cases respectively.

Bhave et al (1983) using chromatography, observed single sugar intolerance in all the cases. In 70% of cases, it was lactose intolerance while glucose and sucrose intolerance was seen in 15% of cases each.

Ashoka et al (1988) reported an incidence of 68% sugar intolerance using chromatography in chronic diarrhoea. Intolerance of lactose with galactose was seen in 36% of cases. Lactose with glucose was seen in 4% of cases. Triple sugar intolerance with lactose, glucose and galactose was seen in 16% of cases. Only monosaccharides were seen in 17% of cases.

Karabocuogles et al (1994) reported an incidence of 11% of carbohydrate intolerance in acute diarrhoea. They observed in 64% cases the sugar was glucose and galactose.

The present study showed that lactose intolerance was predominantly (Table II) a problem of the latter half of infancy. 37.50% of the cases in this study were

between 7-12 months of age with peak incidence at 9 months. In the study conducted by Ghai et al (1982) the peak incidence of carbohydrate intolerance was 10.63 months.

Bhan and Bhandari et al (1989) observed in their study that the incidence of persistent diarrhoea was highest among those aged 0-11 months.

According to Huttly et al (1989) highest incidence of persistent diarrhoea was among children under 6 months of age. Bhan et al (1989) and Ebrahim et al (1990) also stated that mean age of persistent diarrhoea was between 8-9 months of age.

A recent study, Deivanayagam et al (1993) reported that the mean age of children with persistent diarrhoea under 2 years of age was 8.5 months.

That male children are more predisposed to develop lactose intolerance, has been found in several other studies. The male and female ratio as obtained in this study was 2.2:1 (Table III). Trounce et al (1985) found a male to female ratio of 3:2 in case of carbohydrate intolerance.

The male preponderance could be a reflection of the traditional Indian family taking more interest in the male child in all spheres including medical attention. It could also perhaps be explained by the fact that the gene controlling synthesis of immunoglobulin is located on the X chromosome. Since females are

homozygous for X chromosome, they have higher level of immunoglobulin with subsequent higher level of resistance against invasive micro-organisms.

According to table IV, out of 85 cases of chronic diarrhoea, 78.12% cases belonged to the lower socio-economic strata. This is possibly because poverty is associated with malnutrition, higher incidence of infection, lack of education and proper hygiene. Parental ignorance and poverty lies at the root of the problem.

According to table V, 56.25% of the patient in this study had grade II and II malnutrition. 18.75% of grade IV malnutrition and grade I also 18.75% was present. Remaining 6.25% had normal nutrition.

In 18.88% of infants above 11 months of age, grade IV malnutrition was observed. The above results emphasize the increased incidence of malnutrition above 11 months of age, probably associated with weaning diarrhoea and the fact that sugar intolerance can occur in all nutritional groups.

Lifshitz et al (1971) found a positive correlation with increasing severity of malnutrition. Udani et al (1976) reported sugar intolerance in all nutritional groups. Kumar et al (1977) found a high incidence of intolerance in well nourished children. Krause et al (1981) showed 50% incidence of sugar intolerance in well nourished babies after acute [illegible] enteritis. Trounce et al

(1985) reported that malnutrition predisposed to lactose malabsorption after acute enteritis.

Protein energy malnutrition (PEM) is associated with diminished neutrophil function, chemotaxis and phagocytosis, decreased opsonisation, diminished T cell response, diminished secretary IgA level which tend to perpetuate the infection and further aggravate malnutrition. The lower levels of proteins in protein energy malnutrition prevent quick regeneration of destroyed intestinal epithelium.

According to table VI antibiotics had been administered to 87.50% of cases who developed lactose intolerance prior to admission. Kumar et al (1975) reported that 71% of infants had received one or more antibiotics. Davidson (1984) reported that 37% had received antibiotics, perhaps the antibiotics by altering the flora of the intestinal and by destroying the brush border epithelium, also had a role to play in the perpetuation of the diarrhoea. Goulet et al (1995) described the epithelial and basement membrane abnormalities in intractable diarrhoea of infancy in his study. The study revealed villous atrophy with normal or hyperplastic and regenerative cryptae, normal cellularity of lamina - mesenterii propria and no signs of T cell activation. The main histological features are epithelial dysplasia with focal crowding and disorganization of surface enterocyte,

Pseudocystic formation of glands and abnormal regenerative cryptae. On studying the basement membrane components with polyclonal antibodies on frogen specimens they observed that there was faint and irregular deposition of lamina at the epithelium lamina mesenterii propria interface. Whereas deposition of heparan sulfate proteoglycan were large and lamellar. They concluded that modification might be related to epithelial abnormalities and to the severity of this neonatal diarrhoea, which resisted all treatment and necessitated permanent total parenteral nutrition.

Administration of antibiotics indiscriminately during an episode of diarrhoea induces destruction of intestinal epithelium and subsequent sugar intolerance.

Table VII showed breast feeding was the major cause of sugar intolerance. Out of 45 cases more than 50% showed sugar intolerance while only 35% of cases were sugar positive to the patients of lactose intolerance, who received artificial milk alone.

According to table VIII out of 12 cases of lactose intolerance 28.12% of children in this study were on breast feeds alone during the diarrhoeal episodes, while 37.5% received cow's and buffalo milk in addition to breast milk. Since the lactose component of breast milk is higher,,infants on breast milk are probably more prone to develop lactose intolerance. Five children who are exclusively given artificial feeds had also developed

lactose intolerance and 6 children who developed lactose intolerance were on breast milk and semisolids.

The study showed that breast feeding did not protect a child from developing lactose intolerance.

Sazwal et al (1992) reported a much higher risk of persistence of an acute diarrhoea with liquid animal milk than with spray dried infant formula, when compared with breast feeding as the reference risk.

They study does not explain whether the results are related to reduced antigenicity of milk by exposure to high temperature during spray drying or the lower osmolarity and solute load due to the lower lactose content of infant formula.

As is evident in table IX that majority of the children (87.5%) with lactose intolerance had diarrhoea of watery consistency while it was semisolids in consistency in the rest of the cases, under study. Other important symptoms were fever (56.25%), vomiting 43.7%, and abdominal distension 37.50% of cases. Diarrhoea and frequency of stool in sugar intolerance has been attributed to bacterial fermentation of undigested intestinal contents and the osmotic action of large amount of unabsorbed sugar.

Perianal excoriation was found in 75% of cases which was positive for lactose in the present study. Ghai et al (1982) emphasized this fact. However, the severity of perianal excoration did not correlate with

the extent of lactose malabsorption, perianal excoration subsided spontaneously on withdrawal of the offending sugar (lactose).

According to table XI associated systemic disease at the time of admission was seen in 53.12% of cases. Among the majority of the children (25%) were of acute respiratory infection, 12.5% of malaria, 9.37% suffered from encephalitis like illness and remaining 6.25% cases had severe anaemia. However, the disease showed no correlation to the development of lactose intolerance. Systemic disease would have probably contributed to lactose intolerance by necessitating further administration of antibiotics.

Lifshitz et al (1971) emphasized the fact that systemic infection prevented the gut from regenrating destroyed epithelium. Destroyed gut epithelium, besides increasing the higher intolerance, facilitated rapid entry of pathogenic micro-organisms and their toxins into blood stream and produced septicemia, endotoxemia, hypersensitivity to various proteins etc. According to Thapa et al (1994) intractable diarrhoea other associated infections were septicemia (22%), bronchopneumonia (6%), meningitis (4") and urinary tract infection in 3% of cases.

Vitamin deficiency was also shown in the present study. It was shown that out of 32 cases of lactose intolerance only 7(21.87%) were found with vitamin

deficiency. Two cases were of vitamin A deficiency, 4 cases were of vitamin B deficiency and only 1 case of vitamin C deficiency. Thapa et al (1994) observed in their study that about 10% of diarrhoeal cases had evidence of vitamin deficiency.

The microscopic examination of stool showed that stool were greenish yellow with foul smelling and frothy in 75% of cases. Udani et al (1976) emphasized that stool are large, watery at the time of admission greenish or yellow in colour, usually had sour smell and often contained mucus in case of sugar intolerance. Ansari et al (1979) reported that in 76% of cases stool were large, frothy and sour smelling.

Microscopic examination revealed pus cells in 12.5% of cases but no fat globules were detected in any of the cases in present study.

Presence of large numbers of fat globules on stool microscopy in children with lactose intolerance would have suggested concomitant fat malabsorption. Lifshitz et al (1971) reported that steatorrhoea could sometimes be associated with sugar intolerance.

Amoebiasis was seen in 2(6.25%) cases but giardiasis was not seen in any of the case. It is an important protozoa which may cause lactose intolerance and prolongation of diarrhoea. E.Coli was seen in 9.38% of cases while Shigella spc seen only in 1(3.13%) case.

Round worms were seen in present study in 3 (9.38%) cases,,but no hookworm and other parasites could be detected by microscopic examination. Bhan et al(1989) reported established enteric pathogens during initial illness in 46.4% of persistent and 55.4% of acute diarrhoea. Pathogens isolated during persistent episodes include E.Coli (9.3%). Salmonella spp (4.7%),Compylobacter (4.7%), Shigella spp (2.3%), E.histolytica (2.3%) and Rotavirus (2.3%) of cases.

Fat malabsorption could be due to deficiency of the enzyme glycosyl ceremidase which splits glycosyl ceramide present in milk fat vesicles and exists as a complex with lactase, or due to deconjugation of bile salts as a result of colonization of small intestine of anaerobes.

The pH of the stool was found to be a useful guidelines towards the diagnosis of lactose intolerance as observed in the present study. The mean pH of the stool in this study (Table XIV) was 5.5 in 56.25% and 5 in 12.5%, while 25% cases had pH of stool 6. Out of 32 cases 2 cases had pH 4.5.

Durand et al (1961) and Davidson (1967) stated that stool pH of less than 6 was characteristic of disaccharide malabsorption and that was a reliable indicator. Lifshitz (1971) emphasized that stool pH was a reliable indicator. Udani et al (1976) in their study

reported that stool pH was below 6 in 61% of cases. It was also noted by authors that greater the amount of sugar that was detected in the stool lesser was the pH value.

Ansari et al (1979) reported that pH was less than 6 in 67% of cases of sugar intolerance. However, oral intake of furazolidine and neomycin and delay in the performance of test tended to increase the stool pH despite the existence of sugar intolerance. On the other hand infants with metabolic acidosis passed stool with acid pH that gave false positive indication of sugar intolerance.

McMichael et al (1980) reported that stool pH was highly fluctuant and unreliable in sugar intolerance . Bhave et al (1983) also agreed with the above statement of McMichael. However, consensus of opinion at present is that stool pH could be used as a rough and quick screening test for other diagnostic measures to follow.

In present study Benedicts test for reducing agent in stool showed 0.25-0.99 gm% sugar in 35.5% and 1.00-1.99 gm% sugar also in 35.5% of cases while more than 3 gm% sugar was present in 22.33% of cases (Table XIV). However, presence of reducing agent in stool was not synonymous with sugar intolerance as six false positive cases were seen which ultimately did not show evidence of sugar on chromatography.

Udani et al (1976) pointed out that there are

many factors which affected the outcome of this test. During an episode of diarrhoea, if the child is on oral rehydration solution some amount of glucose content in oral rehydration solution would be excreted in stool as a result of intestinal hurry. Moreover, if the lactose deficiency of the intestinal epithelium was only partial, part of the lactose was split into its component monosaccharides that appeared in the stool to give a false positive test with Benedict's reagent. In all cases of present study examination of acid hydrolysed specimen of stool filtrate was done in order to detect sucrose in stool.

In present study table XVII showed that Benedicts test was sensitive in 93.7% but specificity was 86.90% and Rubner's test was sensitive in 90.45% cases and specificity was 93.02% of cases.

It was found in the present study that Benedict's test was more sensitive test as compared to Rubner's test and specificity of Rubner's test (93.02%) was high as compared to Benedict's test (86.9%) i.e. Rubner's test was much specific than Benedict's test.

Singh et al (1991) reported that modified Rubner's test was more specific test for detection of sugar in stool.

In this study oral and lactose loading test was not done, as many authors have pointed out various disadvantages which limit the use of this diagnostic

test. Lactose loading test may result in severe bouts of diarrhoea and requires repeated collection of blood samples, which would be unacceptable to many parents.

Udani et al (1971) pointed out that sugar loading test was rarely necessary in routine practice and would be useful only in cases which showed a clinical picture of sugar intolerance and responded to withdrawal of the sugar from diet, but did not show evidence of sugar in the stool.

Stool chromatography though a very tidious procedure was found to be an excellent, high sensitive and reliable indicator of the presence of sugar intolerance. Even mild degree of sugar intolerance could be detected by this method. In this study lactose alone was observed in 71.1% of cases, 13.3% cases had lactose along with galactose and sucrose intolerance. One case showed lactose with glucose and galactose.

Lactose along with glucose was found in 8.8% and lactose along with sucrose was found in 4.4%. Not more than three sugars were found in any case(Table XVIII and XIX).

Stool chromatography has been hailed as a corner stone. Procedure for the diagnosis of sugar intolerance by Durand (1961) and Hawarth (1963).

Bowie et al (1965) studied acquired disaccharide intolerance in malnutrition. Disaccharide intolerance was

seen in 52% of the cases which were diagnosed by chromatography. The predominant sugars detected were lactose, glucose and galactose in varying amount.

Udani et al (1976) in their study detected by chromatography, lactose in stool 30% of cases and lactose with other sugars in 30% of cases. Sucrose alone was seen in 20% of cases and glucose alone in the remaining 20% of cases.

Karabocuoglu et al (1994) reported that thin layer chromatography when done in conjunction with fecal pH determination and clinitest tablet assay method, was suggested as a useful method in confirming and supplementing the results of these test.

TREATMENT

In the presnt study treatment was given in two groups. One group of 18 patients was kept on soyabased lactose free milk and in second group of 11 cases was treated with antibiotics alone. Remaining three cases were treated with antibiotics along with lactose free formula milk. 50% cases required intravenous therapy. Cases which required other therapy such as antiamoebic and antifungal were not included in this study (Table XX).

It is evident from table XII that out of 18 cases 13(72.3%) cases responded within 5 days of therapy by soya based milk remaining cases responded within 5-7 days. Not even a single case needed therapy beyond more than 7 days.

This study concluded that by withholding the offending sugar lactose the response was 100% within 7 days and the children become symptom free.

Malcolm et al (1965) advocated the practice of withholding milk in protracted diarrhoea.

Soyabeen preparation were suggested as a milk substituted by Hill and Stuart (1980).

Larcher et al (1980), Bhan et al (1983) and Bhave et al (1983) have emphasized that there may be intolerance to low lactose formulae due to associated milk protein intolerance and gluten sensitivity. To cope with such situation, authors have devised some diets prepared from locally available ingredients.

Opinion differs as to when milk diet should be restarted. According to Jeffrey et al (1974) it would be restarted after 10-14 days while Davidson et al (1978) advised a period of at least 4 weeks.

According to Shuh and Walkar (1980) oral feeding should be restarted as early as possible at least partially. The author opines that enteric feedings have a trophic effect on the hypoplastic or damaged intestinal mucosa facilitating early healing and inducing a more rapid return of disaccharidases.

In 1984, Bedline and Boylis suggested that one substrate like glucose could reverse the net secretion and the associated clinical symptoms induced by

malabsorption of another substrate like lactose.

Larcher et al (1984) have made it clear from numerous animal and human studies, that intraluminal food stuffs, carbohydrates and proteins increase intestinal digestive enzyme and cell proliferations in a dose related way, the inductions are some what specific. Sucrose induce sucrase formation, therefore, a mixed carbohydrate diet was most protective against disaccharidase depletion during diarrhoea.

Brunser and Arya et al (1990): cases had to be refed with low lactose products to induce remission of the symptoms, they observed that nutritional parameters were unchanged during and after the diarrhoeal episodes. They suggested that availability of low lactose formula may be advantageous in clinical management of diarrhoea and evidence of lactose intolerance.

Sinden and Sutphan (1991) observed that lactose intolerance children were successfully treated with infant formula, including soya protein and hydrolysate formula in secondary lactose deficiency.

Busino et al (1992) observed that soya based milk was used for different conditions including cow's milk protein allergy and lactose intolerance. Feeding soya protein formula to normal term infants is associated with normal growth, normal protein nutritional status and normal bone mineralization.

According to Bhan and Bhatnagar (1993) 80-90% patients, recovered on initial diet and 10 required change of milk free diet.

Gupta and Gupta (1993) observed that soya based milk formula was commonly prescribed for lactose intolerance secondary to infective diarrhoea. They compared the response between lactose predigested milk feeding and soya milk. They concluded that lactose treated milk was more superior than soya milk for the treatment of lactose intolerance.

Spollett et al (1994) concluded in their study that lactose free diet was most successful therapy in lactose intolerance diarrhoeal patients.

Pitchumoni (1995) stated that once the diagnosis of lactose intolerance was confirmed, simple dietary management may resolve symptoms completely.

Bhutta et al (1995) in their study revealed that a locally available and culturally acceptable rice based diet was at least as effective as soya formula used alone in treating persistent diarrhoea. Although the soya protein based diet are the standard of treatment of persistent diarrhoea in Pakistan. The study revealed greater improvement in weight gain stool volume and frequency in culturally acceptable diet than in soya based formula fed children.

Second group of 11 patients in present study were treated with antibiotics alone. It was seen than only 4(36.4%) children were symptoms free within 5-7 days while rest of the 7 cases when switched over to soya based lactose free diet, all of them responded the therapy within seven days of initiation of soya based lactose free diet. Thus the present study showed that role of antibiotics therapy is not beneficial as compared with lactose free soya milk therapy (Table XXII and XXIII).

A study conducted by Bhan and Bhatnagar et al (1992) revealed that no improvement in purge rate, weight gain or overall illness among children with persistent diarrhoea treated with oral gentamycin than with a placebo. In another study of Bhan and Bhatnagar (1993) only one third of hospitalized patients of persistent diarrhoea, required systemic antibiotics.

Controlled clinical experience with antibiotics therapy is limited. Hill et al (1984) reported beneficial effects with oral gentamycin therapy in persistent diarrhoea. Their strategy allowed selection mainly of cases of severe high purging diarrhoea of more than 5-7 days.

The 3 cases which were treated with combined therapy (soya based milk & antibiotics) also responded within 7 days of therapy.

Antibiotics used in these cases as shown in table XXIV were Amikacin in 7cases (63.6%) out of these 7 cases only 3 responded with amikacin within 5-7 days. and Amikacin along with cefotaxim were given in rest of 4 cases, only 1 case was symptom free within 5-7 days.

The organisms E. Coli and Shigella isolated in this study were sensitive to Amikacin.

The cases were kept on antibiotics alone had other systemic disease also, most of them (25%) had acute respiratory infection. 9.37% of cases had encephalitis like illness and 12.50% c ases had malaria.

Currently, antimicrobial agents may be used in the presence of bloody stools associated with Shigellasis, Giardiasis and amboebiasis should be treated only when a diagnosis of trophozoites is made on microscopy (Bhan et al, 1993).

In the present study, it was concluded that out of 32 cases, only 18(56.25%) cases were treated with soya based lactose free milk alone, and all of them responded to this therapy within 7 days of administration of the soya based milk. On the other hand out of 11(43.75%) cases, only 4 (36.4%) responded with antibiotics within 7 days, while the remaining 7 (63.6%) cases after 7 days antibiotics therapy were switched over to soya based milk therapy. It was seen that all the 7 dases, which

were switched over to soya based milk formula, were symptoms free within next 5-7 days. Rest of 3(9.37%) cases were treated with antibiotics along with soya based milk formula, it was seen that all of them also responded within 7 days of the therapy.

Repeat stool culture was done only in those cases who were culture positive prior to treatment. All of them become sterile after 7 days of antibiotics therapy. Similarly stool pH and lactose sugar by chromatography was repeated after 7 days of therapy, and it was observed that all became lactose free and showed pH more than 6.

Thus, over observations in a nutsheil reveal, that soya based lactose free milk was found to be much diarrhoea showing lactose intolerance than the chronic diarrhoea showing lactose intolerance than the administration of antibiotics alone.

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

The present study was conducted in Department of Pediatrics, Biochemistry and Microbiology, M.L.B. Medical College, Jhansi, for a period of one year from 10.9.94 to 15.9.95. The cases included in this study comprised of children presenting with chronic diarrhoea.

Altogether eighty five children presenting with chronic diarrhoea were studied. Aim of this study was to find out the prevalence of lactose intolerance in chronic diarrhoea, and to assess the efficacy of soya based lactose free formula in lactose intolerance patients and to do a comparative evaluation vis-a-vis antibiotics therapy in the management of cases of lactose intolerance.

In each case a detailed history particularly with regard to diarrhoea, its duration and severity and other complaints were noted. A detailed dietary history regarding the nature of feeds, status of malnutrition was recorded.

The diagnostic procedure employed for detecting lactose intolerance was thin layer chromatography. Prior to that all the screening tests viz. stool pH, stool reducing substance by Benedict's and Rubner's tests were done.

Treatment given to children were kept in 3 groups. One group of 18 patients which were treated

with soya based lactose free milk alone. In second group of 11 children treated with antibiotics (Amikacin) alone and 3 cases were kept on both antibiotics and soya based lactose free formula. Cases who required another additional therapy such as antiamoebic and antifungal were not included in this study.

The results obtained are summarised as follows:

1. The prevalence of carbohydrate intolerance in chronic diarrhoea was 52.35%.
2. The prevalence of lactose intolerance among total patients of carbohydrate intolerance was 71.1%.
3. Lactose intolerance was predominantly a problem of the latter half of infancy, majority of cases(37.5%) occurring in this age group, mean age was 9 months.
4. There was a definite mal preponderance in lactose intolerance with male : female ratio being 2.2:1.
5. Lactose intolerance was predominantly a problem affecting the children in the lower socio-economic strata, 78.12% of cases belonged to this group.
6. Majority of patients (56.25%) in this study had either grade II and III malnutrition. Remaining of the cases were in grade I and IV malnutrition. Only 6.25% cases had normal nutrition.
7. Antibiotics had been administered to 87.50% of cases who developed lactose intolerance prior to admission.

8. In present srudy it was seen that among 85 cases, 56% of cases were on breast feed alone and 35% of cases received artificial milk (cow's/buffalow milk) amone. Remaining of the cases were on breast milk and some semisolid household proprietary preparation. It was concluded in present study that breast fed babies were more prone to develop lactose intolerance.
9. Out of 32 cases of lactose intolerance, 37.5% of cases were on cow's milk or buffalo's milk in addition to breast milk when they developed the problem of lactose intolerance. Another 28.12% of cases were on breast feeds alone. Remaining of cases were on artificial milk and some kind of proprietary preparation.
10. Watery diarrhoea was observed in 87.50% of children suffering from lactose intolerance. Stool frequency was more than 10/day in 56.25% cases. Perianal excoriation was present in 75% of cases of lactose intolerance. Other symptoms viz fever in 56.25%, vomiting in 43.70%, abdominal distension in 37.50% of cases of lactose intolerance.
11. More than half (53.12%) cases had associated systemic diseases viz. acute respiratory infection, encephalitis like illness, malaria and vitamin deficiency. Among them (12.50%) acute respiratory infection was predominant systemic disease.

12. On microscopic examination, stool was greenish yellow, foul smelling and frothy in 75% of cases. Microscopic examination revealed pus cells in 12.5% of cases. Amoeba was seen in 6.25% of cases. Giardia was not seen in any of the case. Ova of round worm were seen in 9.38%m of cases, but no other parasites were seen. Fat globules were also not seen in any of the case. Stool culture revealed organisms predominantly E. Coli in 9.38% of cases while Shigella was seen only in 1(3.13%) case.
13. Stool pH in majority of cases (56.25%) was 5.5. Only 6.25% of cases had pH 4.5.
14. Benedict's test for reducing agent in stool showed 0.25-0.99 gm% sugar in 35.5% and 1.0-1.90 gm% sugar also in 35.50% of cases while more than 3 gm% sugar was present in 22.33% of [illegible] cases.
15. It was also found out in the present study that Benedict's test was more sensitive as compared to Rubner's test in finding out sugar intolerance. It's sensitivity in sugar intolerance was 93.7% as compared to 90.45% in Rubner's test. But Benedict's test was less specific (86.9%) as compared to Rubner's test (93.02%).
16. Stool chromatography was found to be a highly sensitive and reliable indicator for the presence of lactose intolerance. Lactose alone was present in

71.1% of cases. Lactose in addition to glucose was detected in 8.8% of cases and lactose along with galactose and sucrose was detected in 13.3% of cases while in 4.4% of cases lactose was seen in addition to sucrose. Not more than three sugars were present in this study.

Out of 32 cases of lactose intolerance, 18 cases were put on soya based lactose free milk formula, 11 cases were only given antibiotics and remaining 3 cases received both antibiotics and soya based lactose free milk formula. This treatment protocol was done to evaluate the efficacy of lactose free formula, antibiotics and a combination of antibiotics and lactose free formula in management of cases of chronic diarrhoea showing lactose intolerance.

17. 56.25% of cases were treated with soya based lactose free milk, and all of them responded to that therapy within 7 days.
18. 43.75% were treated with antibiotics. Antibiotic used in those cases was Amikacin in 63.6% and Amikacin plus cefotaxim in 36.4% of cases.
19. Out of 43.75% of cases treated with antibiotics, only 36.4% of cases responded with antibiotics therapy within 7 days.

20. Remaining 63.6% of cases who did not respond with antibiotics alone were switched over to soya based lactose free milk. It was seen that all the cases were symptom free within next 5-7 days.

21. Stool culture was positive with E.Coli in 9.38% of cases and Shigell in 3.13% of cases. All stool cultures were sensitive to Amikacin.

22. Three cases treated with antibiotics along with soya based lactose free milk responded within 7 days of therapy.

Thus over observations in a nutshell reveal that soya based lactose free milk was found to be much more beneficial in the management of cases of chronic diarrhoea showing lactose intolerance than administration of antibiotics alone.

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A P P E N D I X

APPENDIX

A COMPARATIVE EVALUATION OF SOYA BASED LACTOSE FREE FORMULA AND PARENTERAL ANTIBIOTIC THERAPY IN MANAGEMENT OF LACTASE DEFICIENT CHRONIC DIARRHOEAL CASES :

Guide : Dr. R.S.Sethi, MD, DCH,
Assistant Professor,
Department of Pediatrics,
M.L.B. Medical College, Jhansi.

Candidate: Dr. Lalit Kumar.

Case No. _____

OPD/MRD NO. _____ Date :

Name of subject : Age/Sex

Address: D.O.A.

Parenteral Occupation: D.O.D.

Birth order of child :

PRESENT HISTORY

Diarrhoea : Duration - Acute (⩽1 week)
- Protracted (7 14 days)
- Chronic (74 weeks).

Severity - Mild (No dehydration)
- Moderate (Mild dehydration)
- Severe(Moderate to Severe dehydration).

Nature of stool : Formed
Semi-solid
Watery

Colour of stool : Yellowish
Greeish yellow
Dark green

Presence of mucus and blood

Anorexia	Fever
Failure to thrive	Vomiting
Abdominal distension	Perianal excoriation
Increased flatulence	Number of motions per day.

PAST HISTORY(H/o similar episodes)

FAMILY HISTORY

1. Hypertension
2. Diabetes
3. Malabsorption

DIETARY HISTORY	From	Upto
a. On breast feeds only		
b. Artificial feeds introduced		
c. Solids introduced		

Nature of artificial milk give	Past	Present
a. Cow's milk		
b. Goat's milk		Diluted
c. Baffalo's milk		Undiluted

Infant formula/Brand/Ratio etc. :

NUTRITIONAL STATUS

Recommended : Proteins Calories

Amount consumed

Malnutrition (IAP Classification) : Grade I - 71.80%
Grade II - 61-70%
Grade III - 51-60%
Grade IV - 50% or below

SOCIO-ECONOMIC STATUS

GENITOLOGICAL HISTORY

ANTIBIOTICS USED

PHYSICAL EXAMINATION

ANTHROPOMETRY

Height : cms. Weight : kgs
Head circumference: cms
Chest circumference: cms
Mid arm circumference: cms.

GENERAL EXAMINATION

H.R. : R.R. : Temp. :

Hair : Lack of lusture
Thin & Sparse
Straightness
Dyspigmentation
Flag sign
Easy pluckability

Face : Diffuse depigmentation
Nasolabial dyssebacea.
Moon face.

Ant. Fontenella : Flush
Depressed

Eyes : Bitot's spots.
Conjuctival xerosis
Corneal xerosis
Keratomalacia
Angular palpepritis
Sunken and dry.

Lips : Angular stomatitis
Angular scars
Cheitosis

Teeth : Mottled Enamel

Gums : Spongy, bleeding gums

Glands: Thyroid enlargement
Parotid enlargement
Lymphonode enlargement

Tongue: Atrophic papillae
Scarlet - oral thrust
Raw tongue

Skin : Follicular hyperkeratosis
Petechiae
Flaky paint dermatitis
Skin turgor.

Nails : Koilonychia

Subcutaneous tissue : Oedema
Amount of subcutaneous fat.

Muscular and Skeletal System
- Muscle waisting
- Craniotabes
- Frontal and parietal bossing
- Epiphyseal enlargement
- Beading of ribs
- Knock knee or Bow legs

G.I.T. Hepatomegaly

Nervous system
- Psychomotor change
- Mental confusion
- Sensory loss
- Motor weakness
- Loss of position sense
- Loss of vibration sense

Cardiovascular System
- Cardiac enlargement
- Tachycardia

INVESTIGATIONS

Stool : Microscopic examination : Ova, cysts, parasites
Culture & sensitivity
pH - at the time of admission :
at the time of discharge :
Stool reducing substances : Precipitate

Greenish yellow	- 0.25-0.99%
Yellow	- 1.00-1.99%
Orange	- 2.00-2.99%
Brick red	- 3% or above

Rubner's test : Positive / Negative

Stool chromatography : Single
Multiple

Type of sugar identified :

Glucose	Maltose
Galactose	Sucrose
Lactose	Fructose

TYPE OF THERAPY GIVEN

a. Cases fed on soya based lactose free formula alone:

Response in days :

pH after response:

Chromatography after response(after 7 days) :

b. Case kept on antibiotics alone :

Response in days :

pH after response:

Repeat chromatography after 7 days. :

Repeat stool culture after recovery. :

c. Case kept on antibiotics alongwith soya based lactose free formula :

Response in days :

pH after response :

Repeat chromatography after recovery. :
